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Distinct Clinical Courses and Shortened Lifespans in Childhood-Onset DNA Polymerase Gamma Deficiency

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Abstract

Background and Objectives

DNA polymerase subunit gamma (POLG) deficiency is likely the most frequent cause of nuclear-encoded mitochondrial disorders. *POLG*-related disorders reportedly constitute a spectrum of overlapping phenotypes from infancy to late adulthood. We retrospectively reviewed natural histories for 40 children carrying biallelic pathogenic *POLG* variants.

Methods

The patients were identified by the French coordinating center for mitochondrial disorders (CARAMMEL), making this a large monocentric series on childhood-onset POLG deficiency.

Results

Three patterns of clinical course and survival were observed, distinguished by main category of symptoms: neurologic, hepatic, and gastrointestinal. A total of 24 patients needed urgent neurointensive care for tonic-clonic seizures, myoclonic epilepsy, and status epilepticus, occasionally precipitated by valproate administration. Other neurologic symptoms included dystonia, cerebellar ataxia, and peripheral neuropathy. We report 6 POLG-deficient patients with polyradiculoneuropathy mimicking subacute Guillain-Barré syndrome and provide postgadolinium MRI evidence of diffuse cranial nerve root and *cauda equina* enhancement, suggesting these disorders have an inflammatory component. Children presenting with enteral nervous system involvement had vomiting, gastroparesis, and chronic intestinal pseudo-obstruction. They had later ages of onset and lived much longer. Primarily, hepatic presentations had the earliest onset and shortest survivals. Secondary hepatic failure was frequently precipitated by valproate administration given before diagnosis to patients with focal impaired awareness seizures or absence of seizures. These POLG deficiencies were often fatal, with age at death ranging from 3 months to

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Glossary

AHS = Alpers-Huttenlocher syndrome; **CIPO** = chronic intestinal pseudo-obstruction; **POLG** = polymerase gamma.

10 years, with a significant difference in survival between the 3 clinical forms; 6 of the 40 children did survive. No genotype-phenotype correlations were found for the 3 clinical course types.

Discussion

The study demonstrates the prevalence of neurologic presentation and the extent of central, peripheral, and autonomous nervous system involvement in 60% of patients. Most of the patients with early onset and rapidly fatal hepatic failure did not live long enough to develop neurologic symptoms. The study revealed a new clinical form of POLG deficiency presenting with neurodigestive symptoms with longer lifespan. We also propose that POLG deficiency should be considered in children presenting with unexplained polyradiculoneuropathy, demyelinating neuropathy, and elevated CSF protein. Finally, valproate administration remains a notable cause of avoidable death in POLG-deficient patients.

Introduction

Multiple disease scenarios reportedly account for mitochondrial disorders, affecting respiratory chain subunits, assembly factors, mitochondrial translation machinery, mitochondrial networks, and DNA/RNA maintenance machinery.[1] DNA polymerase gamma (POLG) deficiency is the main cause of defective mitochondrial DNA maintenance and the most frequent cause of nuclear-encoded mitochondrial disorders.[2-4] POLG, the catalytic subunit of mitochondrial DNA polymerase, is a 140 kDa protein (1,239 amino acids) encoded by the *POLG* gene.[5] This subunit is involved in DNA polymerase activity; 3′-5′ exonuclease activity, for nucleotide proofreading; and 5′-dRP lyase activity, for base excision repair.

POLG-related disorders constitute a spectrum of overlapping phenotypes from infancy to late adulthood.[6] Childhood-onset forms are known to include (1) Alpers-Huttenlocher syndrome (AHS), characterized by childhood-onset progressive and severe encephalopathy with intractable epilepsy and hepatic failure; (2) childhood myocerebrohepatopathy spectrum with developmental delay, lactic acidosis, myopathy, and failure to thrive; and (3) myoclonic epilepsy, myopathy, and ataxia without ophthalmoplegia.[3,7,8]

To further investigate POLG deficiency, as the most common cause of mitochondrial disorders of nuclear origin, we assembled a retrospective monocentric cohort of 40 child patients. Studying their natural histories, disease progression, lifespans, and outcomes, we observed 3 distinct clinical courses.

Methods

In all, 40 previously unreported children (19 boys, 21 girls) carrying biallelic pathogenic *POLG* variants, identified over the past 20 years (2003–2023), were included in this retrospective study. Relying on the databases of molecular genetics laboratories at 3 French public hospitals (Necker, Bicêtre, and Angers) and the efforts of the mitochondrial disease research unit at the Imagine Institute in Paris, France, the children's clinical files were retrieved and independently reviewed by 2 research team members. The following information was collected: sex, family history, birth measurements, age at disease onset, onset symptoms, clinical course, brain MRI and EEG findings, nerve conduction velocity, metabolic/hepatic workup results, and genotypic data on the patients and their parents.

The clinical teams and hospital laboratories involved in the study were affiliated with CARAMMEL, France's national coordinating center for mitochondrial disorders since 2005. All cases included in the retrospective study were discussed, in person or by videoconferencing, during weekly grand rounds held at CARAMMEL. Cases were presented by attending senior and junior physicians using anonymized slideshows, in the absence of the patients and their family members, to an audience including pediatric neurologists, clinical geneticists, specialists of metabolic diseases, biochemical and molecular geneticists, the principal investigator of the Imagine Institute's mitochondrial disease research unit, and the senior pediatric neuroradiologist, commenting on brain MRI images.

Sequence Analysis

POLG coding sequences (NM_002693.1) were analyzed by Sanger sequencing as previously described.[9] For next-generation sequencing (NGS), panels of 380 reported pathogenic genes were used by the hospital laboratories, and exome sequencing was performed by the Imagine research team.

Standard Protocol Approvals, Registrations, and Patient Consents

Our study adhered to the Declaration of Helsinki and was approved by the institutional review boards at each site. Written informed consent was obtained from the respective parents of each patient before genetic testing.

Data Availability

Data presented in this article cannot be made publicly available because they consider patient information. To protect

patient privacy, access to the data can only be made by request from the corresponding author.

Results

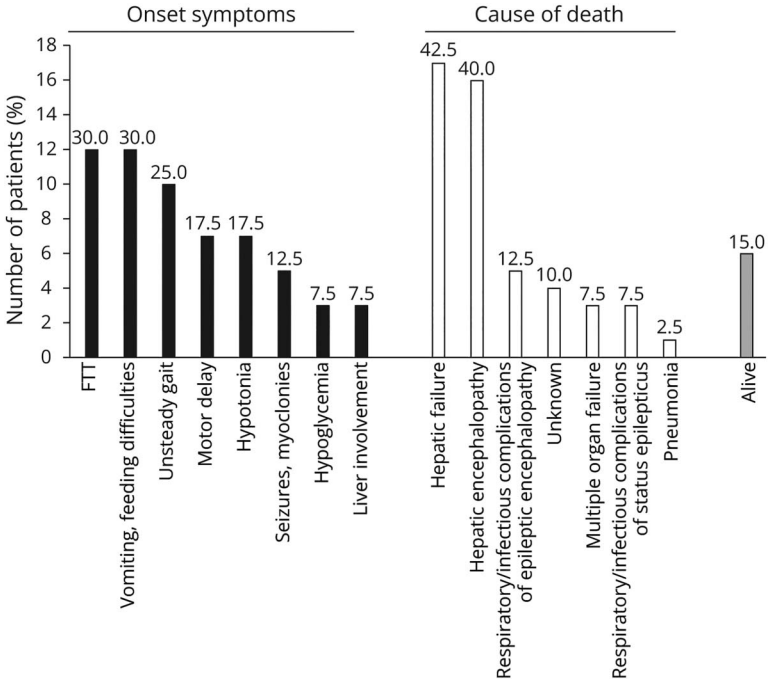
eTable 1 summarizes birth measurements, age at disease onset, clinical course, electrophysiology, brain MRI findings, workup results, genetic data, and outcomes of 40 children with biallelic pathogenic *POLG* variants. All were born at or near term with normal birth measurements and no evidence of intrauterine growth retardation. Age at onset ranged from birth to 5 years (median: 9 months). Disease gradually developed and was ultimately fatal—with a median lifespan after disease onset of 14.25 months (1 month–17 years) and median age at death of 20 months (3–10 years)—for all but 6 of the 40 patients, who were still alive at 4 years 2 months (patient #13), 5 years 6 months (P17), 7 years (P20), 13 years (P32), 15 years (P40), and 17 years (P39) of age, respectively.

Patients were first brought to medical attention for a handful of recurrent onset symptoms, including failure to thrive, motor delay, unsteady gait, vomiting, and seizures (Figure 1). Neurologic or liver involvement occurred shortly thereafter. Figure 2 and eTable 1 show that liver involvement with ascites, hepatic cytolysis, and hepatic failure was prominent in a subset of patients (n = 22) who required urgent rehydration, nutritional support (enteral or parenteral, P35 and P36), and even emergency liver transplants in 3 patients (P7, P26, P32).

A second subset of patients (n = 24) needed urgent neurointensive care for tonic-clonic seizures, myoclonic epilepsy, and status epilepticus, occasionally precipitated by valproate prescribed by professionals unaware of mitochondrial dysfunction as the cause of partial epilepsy (9 patients; see eTable 1). Patients with AHS are reportedly known to present EEG evidence of rhythmic high-amplitude delta activity with superimposed (poly)spikes. Among our subset of neurologic forms, rhythmic activity was explicitly mentioned in 4 of 24 patients and spikes or polyspikes in 10 of 24 patients. Other neurologic symptoms included dystonia, cerebellar ataxia, retinal dystrophy, sensory deafness, and peripheral neuropathy (Figure 2).

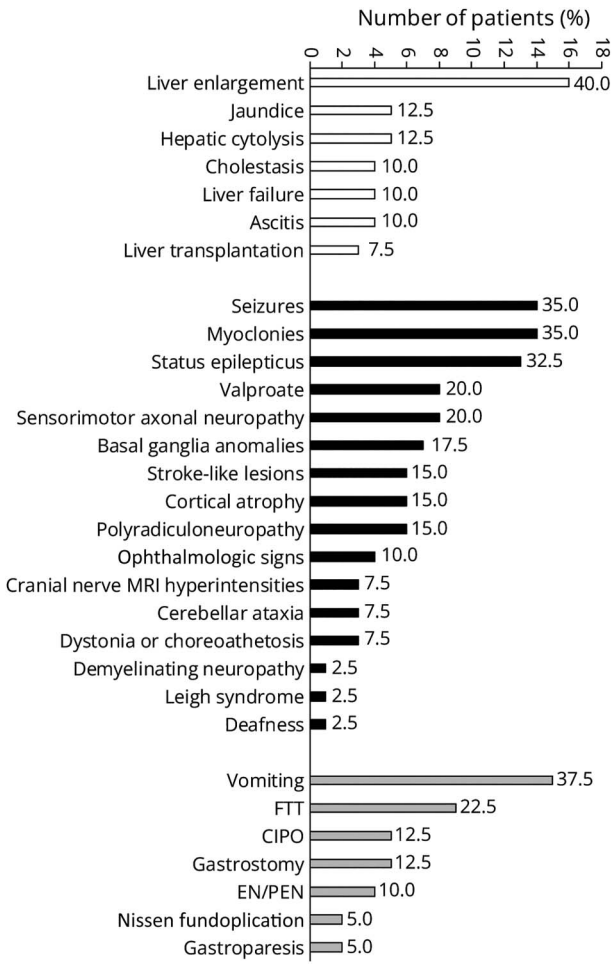
Absence of deep tendon reflexes, general areflexia, polyradiculoneuropathy, and high CSF protein levels mimicking subacute Guillain-Barré syndrome were occasionally noted. When available, nerve conduction velocities provided evidence of sensorimotor axonal neuropathy in 6 patients and myelinic neuropathy in 1 patient (eTable 1). None of the patients presented with quadriparesis, bulbar, or facial palsy. Standard brain and spine MRI results were normal in these patients, but postgadolinium MRI revealed diffuse cranial nerves (III, V, VII, VIII) and *cauda equina* enhancement, suggestive of brain and spinal polyradiculoneuropathy, in 6 patients (P33, P35, P36, P37, P38, P39, Figure 3). Other anomalies detected by standard brain MRI included basal ganglia hyperintensities (8 [patients]), stroke-like lesions (4), nonspecific white matter anomalies (4), cranial nerve anomalies (3), NMR evidence of lactate peaks (4), nonspecific corticosubcortical atrophy (3), and cerebellar atrophy/hypotrophy (3) (eTable 1).

Figure 1 Onset Symptoms and Causes of Death



Onset symptoms and causes of death in 40 children with biallelic pathogenic POLG variants. FTT = failure to thrive. The percentages represent the respective frequencies of each symptom.

Figure 2 Clinical Symptoms



Frequency of clinical symptoms and therapeutic interventions in patients with biallelic pathogenic *POLG* variants. CIPO = chronic intestinal pseudo-obstruction; EN = enteral nutrition; FTT = failure to thrive; PEN = parenteral nutrition. The percentages represent the respective frequencies of each symptom.

Severe digestive tract problems were prominent in 8 patients (P33–P40), who presented with swallowing difficulties, vomiting, gastroenteral reflux disorder, gastroparesis, constipation, chronic intestinal pseudo-obstruction (CIPO), and cachexia; in 1 patient, there was histologic evidence of chronic intestinal inflammation. In all but 1 member of this subgroup, hepatic and CNS involvement was not life threatening. None of the patients with digestive form reportedly displayed EEG evidence of rhythmic activity, spikes, or polyspikes.

Finally, some children were attending, or still attend, special education programs; no hepatocellular carcinoma, major cardiac, or hematologic involvement was observed in our series. Retinal dystrophy, ophthalmoplegia, and cortical blindness were occasionally noted (patients 30, 31, 36, and 37), but ophthalmologic symptoms might have been overlooked owing to the severity of their condition.

Age at disease onset and lifespan were recalculated according to disease form, i.e., primary category of symptoms at initial presentation. Figure 4 shows the Kaplan-Meier estimator of survival according to clinical forms of POLG deficiency. The difference in survival between the 3 clinical forms is significant ($p = 0.004$). The differences between hepatic and digestive forms ($p = 0.006$) and hepatic and neurologic forms are significant ($p = 0.008$). Test for trends between the 3 groups is significant ($p = 0.0025$). In patients with hepatic (H) forms (P1–P8), the median ages of onset and death were much shorter than for patients with neurologic (N) forms (P9–P32) (onset: H, 1.8 months; N, 15.5 months | death: H, 8 months; N, 31.5 months). Of interest, median age at onset for children with digestive (D) disease forms (P33–P40) was intermediate (6 months) while median age at death was much longer (42.5 months), and 2 survivors belong to this group. The 4 other survivors belong to the N group, whereas none of the children from the H group is still alive.

It is worth noting that no D-form patients developed seizures or status epilepticus, and only 1 H-form patient later displayed status epilepticus. Finally, 1 H-form patient (P4) had abnormal EEG findings but never any neurologic symptoms.

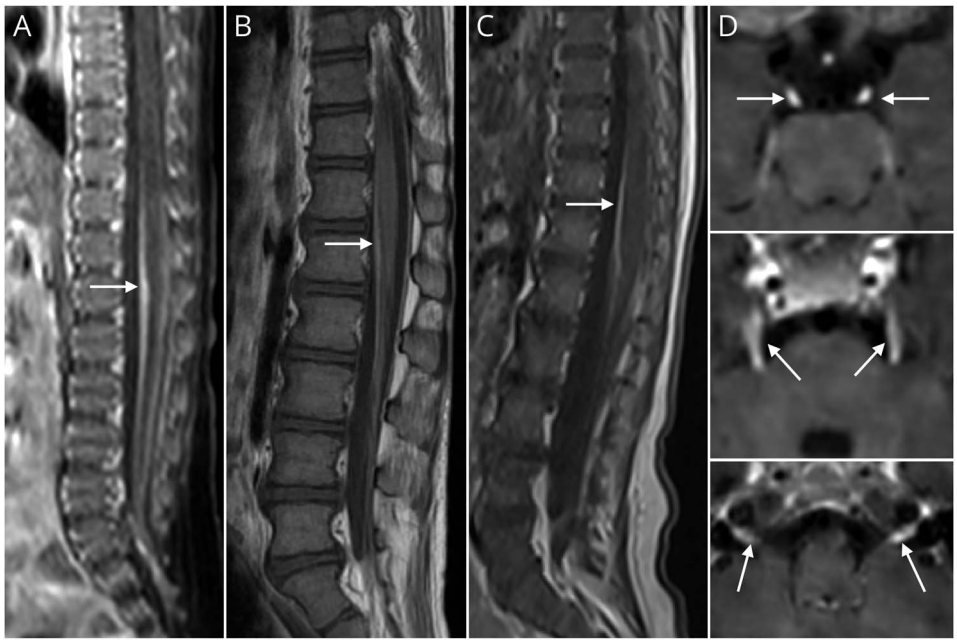
Although nonspecific, plasma lactate (31/35) and CSF lactate (13/15) were almost consistently elevated in our series. The metabolic workup was otherwise nonspecific or contributed little.

In this series, 32 pathogenic *POLG* variants were responsible for the disease: 24 missense, 3 nonsense, and 4 splice site variations, and 1 large deletion (eTable 1 and Figure 5). They were scattered across the exonuclease, polylinker, and polymerase domains of the protein. Three recurrent pathogenic variants were over-represented: p.Ala467Thr in 15 patients, p.Gly848Ser in 10 patients, and p.Trp748Cys in 8 patients. Most of these variants were already recorded in the Human DNA Polymerase Gamma Mutation Database[10] or ClinVar[11]. Previously unreported ones included 1 missense variant (p.Ala1105Val), 1 single amino acid deletion (p.Gly1052del), 2 nonsense or frameshift variants (p.Gly588Profs13 and p.Ile948Asnfs*16), and 2 splice site variants located at the 5′ end of introns 20 and 22. Finally, no genotype-phenotype correlation could be established because no variants were especially associated with a particular clinical form. Moreover, these variations were located in the various clusters previously defined,[12] and no specific combination of heterozygous variations could be identified. All parents were healthy heterozygous carriers of the pathogenic *POLG* variants.

Discussion

We report on the clinical courses of 40 children with biallelic pathogenic *POLG* variants who were identified by the CARAMMEL national mitochondrial disorder coordinating center over the past 20 years. This is, to our knowledge, the largest monocentric cohort of childhood-onset POLG deficiency reported to date. All were born at or near term with normal birth measurements and no signs of intrauterine growth

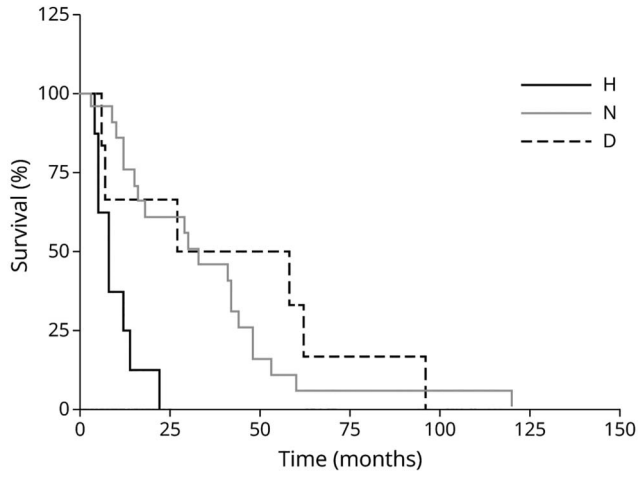
Figure 3 Brain MRI of P33, P36, and P38



Sagittal T1 postgadolinium spine MRI in 3 patients with biallelic pathogenic POLG variants, respectively, aged 3 months (P33, A), 17 months (P36, B), and 16 months (P38, C). Arrows indicate enhancement of the caudal nerve roots. Axial T1 postgadolinium brain MRI in P33 (D) shows (from top to bottom) abnormal enhancement of cisternal oculomotor nerves, cisternal trigeminal nerves, and bilateral intracanalicular facial nerves (arrows).

retardation, suggesting no or little antenatal disease expression. Disease had an early onset, the 5 symptoms most frequently reported in medical records being failure to thrive, feeding difficulties, motor delay, unsteady gait, and hypotonia. Neurologic or hepatic involvement occurred shortly thereafter. The course of the disease gradually worsened and was eventually fatal in most patients (median lifespan after onset: 14.25 months); only 6 patients are still alive.

Figure 4 Survival of POLG Patients



	Hepatic	Neurologic	Digestive
Age at onset	1.8 (0.01–18)	15.5 (0.5–60)	6 (2–36)
Age at death	8 (4–22)	31.5 (3–120)	42.5 (6–96)
Lifespan after onset	4 (3.5–11)	18.5 (1–70)	55 (4–187)

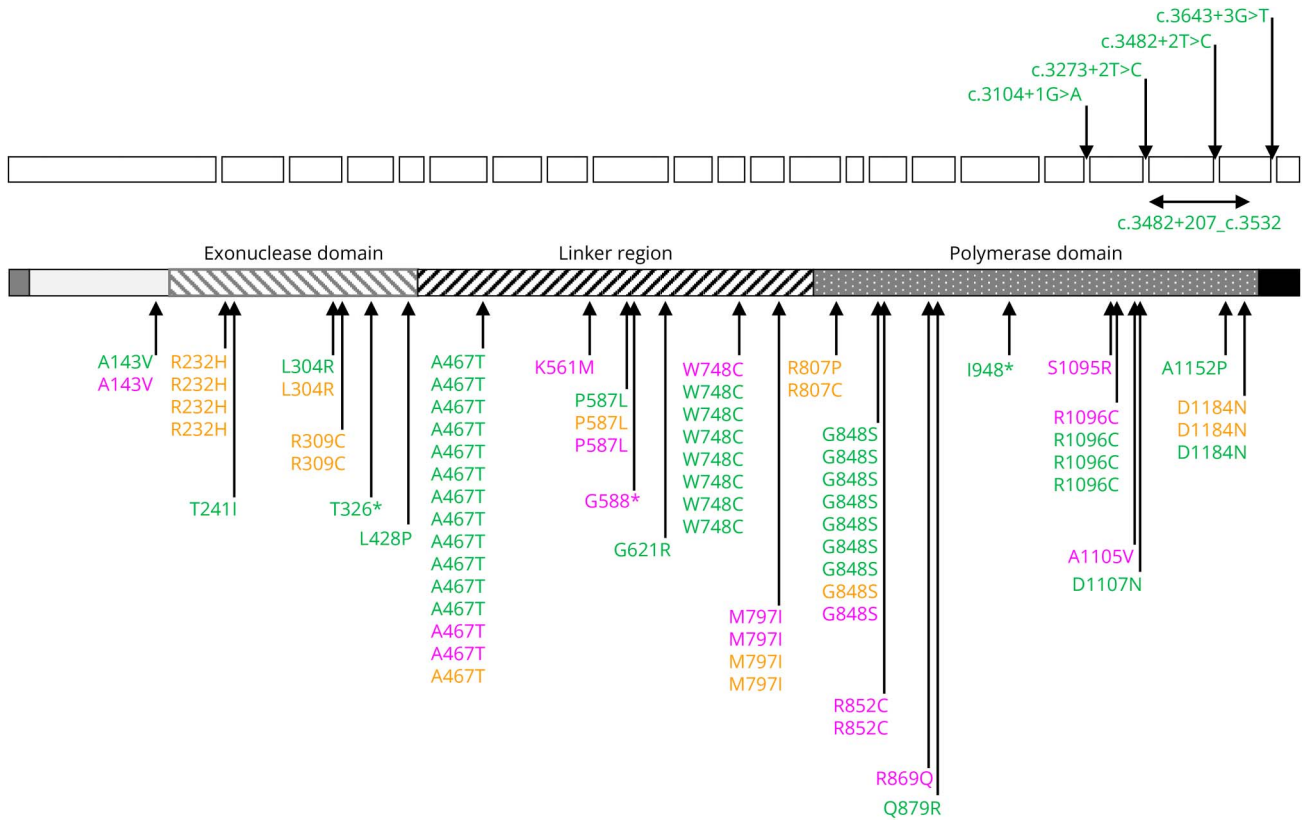
Kaplan-Meier estimator of survival according to clinical forms of POLG deficiency. H: hepatic (n = 8), N: neurologic (n = 24), and D: digestive (n = 8) forms. The difference in survival between the 3 clinical forms is significant ($p = 0.004$). The differences between hepatic and digestive forms ($p = 0.006$) and hepatic and neurologic forms are significant ($p = 0.008$). The difference between digestive and neurologic forms is not significant ($p = 0.01$). Test for trends between the 3 groups is significant ($p = 0.0025$). Median and range of age of disease onset and death are shown below graph.

Several syndromes have been attributed to POLG deficiency[6] including AHS. Although a fraction of patients met inclusion criteria for AHS (triad of refractory seizures, psychomotor regression, and hepatopathy), this seminal description is an imperfect fit for all the pediatric population reported here, notably, the rapidly fatal hepatic forms, the almost purely digestive forms, and polyradiculoneuropathies.[4,13] Indeed, many of our patients could not be ascribed to an existing syndrome or category.

When the cohort was stratified according to prominent symptoms, 3 distinct clinical courses or forms stood out: hepatic (H), neurologic (N), and digestive (D). For H-form patients, median age at onset and lifespans were shorter than for N-form patients. The D form was associated with an intermediate age at onset but a much later median age at death (42.5 months); moreover, there were 2 survivors in this group.

The findings of this study thus support the view that primarily hepatic presentations are associated with the earliest onsets and deaths, all therapeutic interventions, including liver transplants, being ultimately ineffective. The latter could even probably be contraindicated in POLG-related disorder. Nevertheless, 1 patient (P32) had liver transplant at 15 years of age and is still alive, suggesting that transplant at adolescent age can be associated with a better outcome as previously reported.[14,15] A recent report on 1 patient claims that absence of neurologic

Figure 5 *POLG* Mutations



POLG mutations. Top: splice variations and large deletion in cDNA. Bottom: amino acid changes in protein. Recurrent variations associated with neurologic (N), hepatic (H), and digestive (D) clinical courses indicated in pink, green, and orange, respectively.

manifestations could be a good indication for liver transplantation and contribute to a better prognosis.[16] Secondary hepatic failure, frequently precipitated by valproate administration, was responsible for the deaths of 4 of the 9 children with N forms, echoing reports in the literature.[15,17-19] These deaths should be regarded as the consequence of (1) unawareness of mitochondrial dysfunction as the cause of partial epilepsy, (2) misleading MRI patterns mimicking focal cortical lesions, (3) ignorance by prescribers of the toxicity of valproate in oxidative phosphorylation defects, and (4) delayed molecular genetic diagnoses. Nonetheless, 5 of 9 patients receiving valproate did not develop hepatic dysfunction.

This study also demonstrates the extent of central, peripheral, and autonomous nervous system involvement in these patients. Peripheral neuropathy with the absence of deep tendon reflexes[3,7,19,20] and cranial nerve and cervical root enhancement have occasionally been reported in POLG deficiency.[21,22] Our study gives additional support to the view that POLG-deficient patients may present with chronic inflammatory demyelinating polyradiculoneuropathy and provide postgadolinium MRI evidence of diffuse cranial nerve root (III, V, VII, VIII) and *cauda equina* enhancement in 6 patients. Note that findings of standard MRI were unremarkable in our series; only postgadolinium MRI detected brain anomalies, suggesting these disorders have an inflammatory component whose origin is still unknown. We propose that a diagnosis of POLG deficiency should be considered in children presenting with unexplained polyradiculoneuropathy, demyelinating neuropathy, and elevated CSF protein.

Similarly, although vomiting, swallowing difficulties, gastroparesis, or CIPO have occasionally been reported in adulthood[2] and childhood,[7,8] this study offers strong evidence of autonomous nervous system involvement in childhood POLG deficiency. Histologic signs of bowel inflammation in a patient with gastroparesis and CIPO support the view that inflammatory anomalies of hitherto unknown origin may play a role in the pathophysiology of this deficiency. It remains to be explained why a subset of patients primarily presenting with digestive symptoms lived longer (median age 42.5 months) and displayed hepatic and CNS involvement of far less concern. No specific pathogenic variants were matched with this form or any particular clinical presentation.[4]

Finally, one of the limitations of this study is the retrospective nature of the data collection because some clinical data could not be ascertained. Future prospective studies will hopefully allow to systematically record presenting symptoms, brain MRI after injection, and missing biological parameters (such as plasma

α-fetoprotein). The heavy toll paid for administration of valproate in our study raises the issues of adequate medical information and how best to educate general pediatricians and specialists on the deadly risk of prescribing this drug in *POLG*-related disorder.

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Continued

Appendix *(continued)*

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Karine Mention, MD	Centre de référence des Maladies Héréditaires du métabolisme, Hôpital Jeanne de Flandre, Lille, France	Major role in the acquisition of data
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Laurent Pasquier, MD, PhD	Service de Génétique Clinique, CRMR anomalies du développement CLAD-Ouest, Rennes, France	Major role in the acquisition of data
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Nathalie Boddaert, MD, PhD	Centre de Référence des Maladies Mitochondriales; Imagerie pédiatrique, AP-HP, Hôpital Necker-Enfants Malades, Université Paris Cité, France;	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
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